Remarks

Claims 1-8 are currently pending and under examination. Applicants appreciate the Examiner's withdrawal of the restriction requirement entered under PCT Rule 13.1 and 13.2 in the Office Action dated April 23, 2008.

The specification has been amended to claim the benefit of a prior-filed application under 35 U.S.C. 119(e). This information concerning the priority benefit claim was recognized by the Office on the first filing receipt dated January 16, 2007. Therefore, Applicants have filed this amendment to the first sentence of the specification in compliance with 37 CFR 1.78 (a).

Applicants understand that the information disclosure statement (IDS) submitted on 21 July 2006 is in compliance with the provisions of 37 CFR 1.97 and has been considered by the examiner.

Arguments

Claims 1-8 are rejected under 35 U.S.C 103(a) as being unpatentable over Glasebrook *et al.* (WO03/011213) in combination with Hauner (Diabetes Metab. Res. Rev. 18: S10-S15, 2002). Applicants respectfully disagree with this rejection and traverse it based on the following factual argument.

The Examiner states that it would have been *prima facie* obvious at the time of the instant invention to combine the teachings of Glasebrook *et al.* and Hauner and treat type 2 diabetes and/or metabolic syndrome with the combination of FGF-21 and a TZD (such as rosiglitazone and pioglitazone) in order to improve insulin sensitivity and glucose uptake in the individual being treated. Furthermore, the Examiner states that one would be motivated to use the combination of FGF-21 and TZDs for the treatment of type 2 diabetes (or metabolic syndrome) because TZDs increase insulin sensitivity and FGF-21 has a greater effect on glucose uptake in the presence of insulin. Finally, the Examiner states that because the two drugs act via different mechanisms, it is not unexpected that the combination might produce a better effect than either drug alone or as a simple addition of their effects.

Applicants acknowledge the Examiner's assessment of the Hauner reference and the activity and mechanism of TZD's, but allege that the Examiner has misinterpreted the teachings of Glasebrook *et al.* and more importantly, the data exemplified in the present application.

The recent Supreme Court decision in *KSR (KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727,(2007)*) reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)). Objective evidence relevant to the issue of obviousness may include "secondary considerations" such as unexpected results. *Id.* at 17-18, 148 USPQ at 467.

The Examiner interpreted Glasebrook *et al.* as teaching that FGF-21 has a greater effect on glucose uptake in the presence of insulin and combined this fact with Hauner's teaching that TZDs increase insulin sensitivity to establish a *prima facie* case of obviousness for the efficacy of the combination of the two drugs. Applicants point the Examiner to Glasebrook *et al.*, p.10, lines 7-9, where it is stated that "Additionally, FGF-21 stimulates glucose uptake in 3T3-L1 adipocytes in an ***insulin independent*** manner (Figure 3), indicating that it is useful for treating Type 1 diabetes as well." (emphasis added) Furthermore, Figure 3 of Glasebrook *et al.*, shows FGF-21 stimulation of glucose uptake in 3T3-L1 adipocytes in a concentration dependent manner, in the **absence** of insulin. (emphasis added)

By clarifying the teachings of Glasebrook *et al.*, Applicants have rebutted the premise of the Examiner that it would be expected by a person of ordinary skill in the art that a combination of FGF-21 and TZDs would produce a synergistic effect because as the Examiner stated "TZDs appear to enhance a response that is known to enhance the response of FGF-21 (namely glucose uptake in the presence of insulin wherein TZDs increase insulin sensitivity)." Since the mechanism of FGF-21 is insulin independent as taught by Glasebrook *et al.*, this conclusion by the Examiner is incorrect.

The definitive data that shows unexpected results is exemplified in the present application on pp.15-18. For example, the Examiner is directed to Table 1 and Table 2 on p. 15 of the present application. In Table 1, the combination of FGF-21 and rosiglitazone results in an

increased potency in the glucose uptake assay as shown by a greater than two-fold reduction of the ED_{50} (1.7nM to 0.7nM) when compared to FGF-21 alone. Importantly, this assay is performed in the **absence of insulin** as verified in the specification beginning on p.14, lines 31-34, and p.15, lines 5-9. Even more unexpected is the data in Table 2. Here, rosiglitazone is titered from 0 to 10μM and combined with FGF-21 at a constant concentration of 50nM. The rosiglitazone alone has **no effect** on glucose uptake in 3T3 cells, even at the high concentration of 10μM. However, the combination of rosiglitazone and FGF-21 resulted in a synergistic effect that was almost 3X the effect of FGF-21 alone on glucose uptake. Clearly, it is surprising that when a compound that alone has no effect (rosiglitazone) is combined with a compound that is known to be effective (FGF-21) results in an enhanced or synergistic effect in the assay. A person of skill in the art would not predict or expect such a result and therefore such an effect can not be obvious under the framework outlined in *Graham v. John Deere Co.*

Conclusion

Applicants assert that the obviousness rejection under 35 U.S.C. §103 has been overcome by a factual argument that definitively demonstrates surprising and unexpected results with the combination of FGF-21 and TZDs in both *in vitro* and *in vivo* assays. Furthermore, the data exemplified in the present application shows an unexpected synergistic effect on glucose uptake with the combination treatment of FGF-21 and the TZD rosiglitazone.

Applicants respectfully request favorable reconsideration of the present invention as presently claimed and in view of the arguments presented herein.

Respectfully submitted,

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